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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,180	08/11/2006	Nicola La Monica	ITR0073YP	3924

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,180	LA MONICA ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10-16,20 and 21* is/are pending in the application.

4a) Of the above claim(s) *14-16,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,8 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/11/2006;03/24/2009;11/24/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 4-5, 8, 10-16, 20-21 are pending. Claims 3, 6-7, 9, 17-19 and 22-35 are canceled.

Applicant's election with traverse of group I, claims 1-2, 4-5, 8, 10-13 in the reply filed on 11/24/2009 is acknowledged. The traversal is on the ground(s) that the groups I, II and III share the same or special technical feature. This is not found persuasive because the related products of groups I and II as discussed previously the inventions as claimed the vector of group II can be used for in vitro studies of the CEA nucleic acid. The CEA nucleic acid of group I can be used for drug screening in a mammal. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Furthermore, the inventions of group's I-II and III are related as product and process of use and in the instant case the compositions of the group's I-II are patentably distinct each from the method of the group III because the method cannot be used to produce the compositions. Alternatively, the composition may not be used in the methods or will be used in more than one method. Therefore, the inventions of the group's I-III are patentably distinct each from the other and will require separate and non- coextensive searches in the patent and non-patent literature. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Applicants argue to examine group I and II because all of the Group II claims are dependent on claim 13, which is indirectly dependent on claim 1. Thus, all of the features of claim 1 are required in the Group II claims. These arguments are not persuasive because for example group II requires a host cell comprising the vector which is structurally distinct from the nucleic acid of group I. Groups I and II recite divergent subject matter therefore there is undue burden to search and examine claims in both Groups I and III together in the same application. The prior art applicable to one

invention would not likely be applicable to another invention. The inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. The requirement is still deemed proper and is therefore made FINAL.

Claims 14-16, 20-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/24/2009.

Claims 1-2, 4-5, 8, 10-13 are under consideration.

Applicant's election of species CEA-LTB fusion protein for claim 1 and it dependent claims; human CEA protein or variant thereof for claim 2; SEQ ID NO: 12 for claim 10 and Ad6 for claim 16 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 recites the limitation "LT subunit B" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-2, 13** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Rice et al** (The Journal of Immunology, *1*67: 1558-1565, 2001(IDS)) in view of **Arrington et al** (Journal of Virology, 76(9): 4536-4546, 2002 (IDS)).

Rice et al teach DNA fusion vaccine encoding the CEA CTL epitope $CEA_{526–533}$ fused to the fragment C (FrC) DOM amino terminus of tetanus toxoid adjuvant (pDOM-CEA), injected into mice, and high levels of cytolytic activity (CTL) activity was induced with IFN-γ-containing CD8+ T cells (p 1662, 2nd column, 2nd paragraph) and its implications for cancer treatment (title) **(claim 1).** Rice teaches human CEA (p 1562, 2nd column, 2nd paragraph) **(claim 2).** Rice suggests DNA vaccination offers a strategy to induce immune attack on cancer cells, and inclusion of a "foreign" protein such as of tetanus toxoid increases immunogenicity (abstract). Rice teaches fusion of the FrC of tetanus toxin to a tumor Ag sequence promotes Ab and CD4+ responses against B cell tumors (abstract). In addition, Rice teaches inclusion of the leader sequence of the FrC should ensure that all constructs longer than 60 aa are cotranslationally transported into the endoplasmic reticulum (ER) (p 1563, 2nd column, 1st paragraph). Rice teaches antigenic peptides are preferentially produced from the C terminus of precursor peptides in the ER site (p 1563, 2nd column, 1st paragraph) **(claim 13).**

However, Rice does not specifically teach fusion of the CEA to a subunit B of heat labile enterotoxin of E.coli (LTB), in order to induce an immune response in a mammal. However, prior to the time of the claimed invention, **Arrington et al** (Journal of Virology, 76(9): 4536-4546, 2002) teach the heat labile enterotoxin of E. coli (LTB) containing the signal peptide coding sequence is a strong adjuvant for DNA vaccines (title and p 4543, 1st column, 1st paragraph). In addition, Arrington teaches deletion of the signal peptide coding sequence resulted in loss of adjuvant effect, as would be expected since the LTB subunit needs to be outside the cell in order to engage its receptors (p 4543, 1st column, 1st paragraph).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Rice to utilizing subunit B of heat labile enterotoxin of E.coli (LTB), such as that taught by Arrington, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to replace the FrC with the heat labile enterotoxin of E.coli (LTB) as taught by Arrington fused to the CEA CTL epitope $CEA_{526–533}$, in order to increase the adjuvant activity of the CEA vaccine such as suggested by Arrington. One of ordinary of skill in the art would have been motivated to use the C-terminal end of CEA because Rice teaches Rice teaches

antigenic peptides are preferentially produced from the C terminus of precursor peptides in the ER site.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims **1, 8** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Rice et al** (The Journal of Immunology*, 1*67: 1558-1565, 2001) in view of **Arrington et al** (Journal of Virology, 76(9): 4536-4546, 2002) and further in view of **Lund et al,** (Cancer Gene Therapy, 10: 365-376, 2003 (IDS)).

The teachings of Rice and Arrington apply here as indicated above.

However, Rice taken with Arrington does not specifically teach truncation of the LTB signal sequence.

However, at the time of the instant invention **Lund et al,** teach that signal sequence deletion and fusion to tetanus toxoid epitope augment antitumor immune responses to human CEA plasmid DNA vaccine in a murine test system (title). In addition, Lund teaches CEA contains signal peptides that target the protein through the endoplasmic reticulum and to the cell membrane (abstract).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): “Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve

similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Rice/Arrington to deleting the signal sequence of LTB, such as that taught by Lund, in the plasmid LTB-CEA DNA vaccine of Rice/Arrington, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to deleting the signal sequence from the LTB in a CEA vaccine in order to increase the antitumor immune response of the CEA such as suggested by Lund. Although Arrington teaches deletion of the LTB signal peptide coding sequence resulted in loss of adjuvant effect, as would be expected since the LTB subunit needs to be outside the cell in order to engage its receptors (p 4543, 1st column, 1st paragraph) one of skill in the art would readily recognize that deletion of the LTB signal sequence wherein the LTB is fused to the CEA it would result in bringing the LTB subunit without its own signal sequence outside the cell in order to engage its receptors to act as an adjuvant since Lund teaches CEA contains signal peptides that target the protein through the endoplasmic reticulum and to the cell membrane (abstract).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims **1, 4** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Rice et al** (The Journal of Immunology, *1*67: 1558-1565, 2001(IDS)) in view of **Arrington et al** (Journal of Virology, 76(9): 4536-4546, 2002 (IDS)) and further in view of **Klysner,** (US 20050063952 A1 (IDS)).

The teachings of Rice/Arrington apply here as indicted above.

Rice/Arrington neither does nor specifically teaches the CEA protein is C-terminally truncated.

However, at the time of the instant invention **Klysner** teaches it is of high importance to note that CEA naturally has a GPI anchor, meaning that by preserving this in the modified molecule, the self-adjuvating effect would be a possibility and by including this known signal sequence also in constructs that do not include the C-terminus of CEA, it will be achieved that the resulting expression product is anchored to the membrane [0132]. **Klysner** teaches a method for inducing an immune response against autologous carcinoembryonic antigen (CEA) in an animal, including a human being, the method comprising effecting uptake and processing by antigen presenting cells (APCs) in the animal or of a nucleic acid encoding the modified CEA polypeptide or of a pharmaceutically acceptable microorganism or virus expressing the modified CEA polypeptide, said at least one modified CEA polypeptide comprising at least about 80 CEA-derived amino acids, either in the form of at least about 80 consecutive CEA-derived amino acids or in the form of at least about 80 amino acids constituted of uninterrupted CEA-derived CTL epitopes, and at least one first T helper epitope foreign to the animal, thereby inducing a CTL response and/or an antibody response that targets the autologous CEA (p 53 column 1, claim 1) wherein the C-terminal GPI-anchor of CEA is removed (p 54,column 1, claim 21)

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459

(1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Rice/Arrington to substitute the CEA CTL epitope $CEA_{526–533}$ of Rice with the C-terminal GPI-anchor of CEA removed, such as that taught by **Klysner**, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to induce an immune response against autologous CEA in an animal, including a human being, by effecting uptake and processing by antigen presenting cells (APCs) in the animal of a nucleic acid encoding the modified CEA polypeptide constituted of uninterrupted CEA-derived CTL epitopes, and at least one first T helper epitope foreign to the animal, thereby inducing a CTL response and/or an antibody response that targets the autologous such as suggested by **Klysner**.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Allowable Subject Matter

Claims **5, 10-12** are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Magdalene K. Sgagias, Ph.D.
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/Anne-Marie Falk/
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